# Nulliparity, Decade of First Birth, and Breast Cancer in Connecticut Cohorts, 1855 to 1945: An Ecological Study

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Abstract: Risk of breast cancer increases with age at first birth, and is lower in women who bear their first children while young than in nulliparous women. While previous studies have investigated risk of breast cancer in birth cohorts by examining partial aspects of cohort childbearing, the present ecological study assesses total cohort childbearing risk in Connecticut women born between 1855 and 1945. In each cohort, the proportion of women nulliparous and first bearing children in their twenties, thirties, and forties are weighted by relative risks associated with these events as ascertained

in previous studies. Summed cohort childbearing risks are compared to the incidence of breast cancer in women 40 years of age and older in the same cohorts. Changes in decade of first birth and nulliparity do not explain the changes in breast cancer incidence observed: while cohort childbearing risk has declined over the period examined, breast cancer incidence has increased in the same cohorts. Alternative explanations for cohort increases in breast cancer incidence are reviewed. (Am J Public Health 1989; 79:1503–1507.)

## Introduction

In the United States, Europe, and elsewhere, breast cancer incidence and mortality reached a low point in women born at the turn of the twentieth century and have been rising steadily in cohorts born thereafter.<sup>1,2</sup> The predominance of cohort effects in accounting for these secular changes in breast cancer incidence and mortality was noted early by MacMahon,<sup>3</sup> and has been well established by the modeling methods of indirect standardization.<sup>1,2,4,5</sup> MacMahon hypothesized that these cohortwise changes in incidence and mortality might correspond to changing patterns of childbearing.<sup>3</sup>

With several exceptions, 6-8 most case-control studies 9-13 have demonstrated that a woman's risk of breast cancer increases with the age at which she completes her first full term pregnancy. The risk of breast cancer in women first bearing a child before age 18 is estimated to be one-third that of women first bearing after age 34. Nulliparity is associated with greater risk of breast cancer than bearing a first child up to age 34, after which the risk associated with first births exceeds that of nulliparity. A large retrospective cohort study 14 further supports these results.

Several studies 7,15-20 have examined the association of

changing population childbearing patterns with changing patterns of breast cancer incidence and mortality. Using summary vital records from England and Wales, Connecticut, and the United States, MacMahon<sup>15</sup> examined the association of cohort fertility and breast cancer incidence and mortality; findings contradicted the hypothesis that fertility was inversely associated with breast cancer rates. In contrast, Armstrong16 examined proportions of women in the US bearing first children by certain ages and live birth rates by certain ages in England and Wales; he found that childbearing trends accounted at least in part for the cohort variation in breast cancer incidence (in Connecticut) and mortality (in the US and in England and Wales). Likewise, Blot<sup>17</sup> found parallels between proportions of US women nulliparous between ages 20-24 and breast cancer mortality in the same cohorts. Wigle<sup>18</sup> also demonstrated associations between

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marital and fertility characteristics of Canadian women and their rates of breast cancer incidence and mortality. On the other hand, based on correlations among rates of breast cancer mortality among single and married women in nine nations and regions within them, Hems and Stuart<sup>19</sup> claimed that international differences in breast cancer mortality were associated with diet but not with fertility. Most recently, White<sup>20</sup> predicted that delayed childbearing in cohorts of women born since 1945 will yield breast cancer incidence significantly greater than that of preceding cohorts, in which early childbearing was more common.

Other than White's predictive analysis, these studies have shortcomings of two sorts. Some<sup>7,15</sup> have examined risk factors tangential to those now recognized to be associated with rates of breast cancer, for example, cohort fertility by older ages, and proportions married at 20-24 and at 40-44 years. Further, all of these studies examine one or several aspects of cohort childbearing events, e.g., nulliparity between ages 20 and 24, first birth by certain ages, but not the overall cohort history of childbearing. Investigation of isolated elements of cohort childbearing may mask other cohort childbearing risk factors for breast cancer which either support or oppose the particular cohort risk factor investigated. For example, while one cohort may have apparently greater risk than another cohort because of high nulliparity in ages 20-24, it may also have lower risk than the other cohort because of a high rate of first births to women younger than 20 years. Apparent associations and non-associations between partial cohort childbearing events and breast cancer outcomes may thus be misleading.

The present study used vital records and Connecticut Tumor Registry data to examine the association between total cohort childbearing history—nulliparity and decade of first birth—and breast cancer incidence in the population of Connecticut women born between 1855 and 1945.

#### Methods

Information on cohort childbearing events was abstracted from the Connecticut Vital Statistics Report (1879–1945),<sup>21</sup> Vital Statistics of the United States (1946–1982),<sup>22</sup> and the US Census of Population (1880–1980).<sup>23</sup> Information on breast cancer incidence in Connecticut women, ages 20 to 79 years, from 1935 to 1982 was provided by the Connecticut Tumor Registry,<sup>24</sup> as reported in Stevens, *et al*,<sup>2</sup> and updated.

#### Cohort Decades of Firth Birth and Nulliparity

Because Connecticut Vital Statistics Reports present information on women bearing their first children in time intervals of varying length, but commonly in 10-year age categories, e.g., between ages 20 and 29, the present investigation is constrained to a comparison of decades of first birth. Numbers of women bearing first children in each year were aggregated into 10-year groupings centered on decade years (in which Census data were gathered), e.g., 1885–1894 (with decade mid-year 1890), 1895–1940 (mid-year 1900), etc. Since Connecticut Vital Statistics Reports were first published only in 1879, information on first births at different ages in the 1880 "mid-year" was aggregated from 1879 to 1884.

Proportions of women bearing first children in their second, third, fourth, and fifth decades were calculated by dividing numbers of first births in each age group by the population of that group. Since vital registry data on first births for the first Census period (1880) were available only for six of the 10 years in one interval (1879–1984), the proportions of 2nd to 5th decade first births for this period were estimated by dividing the numbers of births by 6/10 of the appropriate Census figures for each age group.

Resultant proportions were reorganized according to the year of birth of the mothers. Thus, proportions of women who bore a first child in their second decade (i.e., ages 10–19) between 1879 and 1884 were associated with those who first bore in their third decades (i.e., 20–29) between 1885 and 1894, and with those who first bore in their fourth decades (i.e., 30–39) between 1895 and 1904, and so on; all of these women were born between 1855 and 1874, a 20-year span referred to by its mid-year as the cohort of 1865.

While a few women were reported to bear first children after age 50, for the purposes of this analysis it was assumed that a women who had not borne a first child by age 50 was nulliparous. Cohort nulliparity was calculated by subtracting from *one* the sum of proportions of cohort women who had borne a first child in their second through fifth decades. That is,

Cohort Nulliparity = 
$$1 - (FB_2 + FB_3 + FB_4 + FB_5)$$
,

where  $FB_n$  = proportion of cohort women bearing a first child in their  $n^{th}$  decade.

## Cohort Childbearing Breast Cancer Risk

Cohort proportions of women nulliparous or first bearing children in different decades were weighted by the relative risks ascribed to these childbearing events by the multination case-control study of MacMahon, et al.<sup>10</sup>

In order to make the relative risks of five-year age groups from the multi-nation the present study, a mean of relative risks within decades was taken to estimate the relative risk for each decade. Since women older than 40 contributed less than 0.5 percent of cohort first births, their contribution to childbearing risk was no longer considered. The total nulliparity and first birth decade risk of breast cancer in cohorts was then estimated by summing the relative risks specific to each childbearing category, weighted by the proportions of each childbearing category in the cohort. That is,

Childbearing Breast Cancer Risk =  $FB_2 \times RR_2 + FB_3 + FB_4 \times RR_4 + Proportion Nulliparous \times RR_{Nulliparity}$ 

where, as above,

 $FB_n$  = the proportion of cohort women bearing a first child in their  $n^{th}$  decade,

and where,

RR<sub>n</sub> = the risk of breast cancer given this event, relative to nulliparity.

## **Breast Cancer Incidence and Standardized Incidence Ratios**

Since the first birth "exposures" considered were those occurring to cohort females by age 40, only breast cancer incidence after this age was analyzed as a possible outcome. Incidence data for women older than 40 years were grouped into 10-year age categories, and arrayed by cohort to parallel available information on childbearing exposures. The number of cases divided by the corresponding sum of womanyears at risk gave the incidence of breast cancer in this group during this period.

To compare cohort experience of breast cancer incidence and changes of breast cancer incidence between cohorts, we computed an aggregate incidence measure for the cohort. Since age-specific data are missing in the youngest cohorts, the usual methods of direct and indirect standardization do not apply. Following the method of Breslow and Day, we computed an internally standardized incidence ratio for each cohort. The method assumes that age effects are constant in all cohorts, and cohort effects constant for each age; both parameters are estimated for all ages and all cohorts by assuming their constancy in cells for which no data are available. It is assumed that the populations are large, and that disease events are rare and well characterized by the Poisson distribution. Further, the expected number of events (incident cases of breast cancer) in age group i and birth cohort j is assumed to be  $E_{ij} = N_{ij} \times a_i \times b_j$ , where  $N_{ij}$ is the population (woman years) at risk in age group i and cohort j, ai is the effect of age group i, and bi is the effect of birth cohort j. The parameter, b<sub>i</sub>, can be thought of as an internally standardized incidence ratio. Maximum likelihood procedures are then used to estimate the parameters of the model. This method yields a summary incidence ratio for cohort data derived from cross-sectional studies.

## Results

# Cohort Childbearing Breast Cancer Risk

For all cohorts of Connecticut females born between mid-years 1865 and 1935, the largest proportion of women have borne a first child in their third decade; the second largest proportion are nulliparous, except for women born in mid-year 1935; the smallest proportions have borne first children in their 2nd or 4th decade (Table 1). Together, cohort proportions of women either nulliparous or first bearing children in their third decades account for between 72 percent and 83 percent of cohort women. Predominant cohort trends are the large, though irregular, increase in the proportion of women bearing their first children in their twenties and the correspondingly large decline in nulliparity.

Weighting of cohort childbearing proportions by the corresponding relative risks yielded a cohort childbearing breast cancer risk profile (Figure 1) indicating: a general declining trend from earlier to later cohorts, interrupted by a small increase from the cohort of 1865 to that of 1875, and a larger increase from the cohort of mid-year 1895 to that of 1905. These risk estimates correspond mainly to changing proportions of third decade first births and nulliparity. Similar

TABLE 1—Proportions of Connecticut Women Nulliparous and First Childbearing in Different Decades (2nd-4th) by Birth Cohort Mid-Year, 1865–1935

| Cohort<br>Mid-Year<br>of Birth | Nulliparas | Woman's Age at First Childbirth |       |       |
|--------------------------------|------------|---------------------------------|-------|-------|
|                                |            | 10–19                           | 20-29 | 30–39 |
| 1865                           | 0.33       | 0.11                            | 0.46  | 0.09  |
| 1875                           | 0.36       | 0.10                            | 0.44  | 0.09  |
| 1885                           | 0.28       | 0.10                            | 0.51  | 0.10  |
| 1895                           | 0.26       | 0.12                            | 0.53  | 0.08  |
| 1905                           | 0.30       | 0.13                            | 0.43  | 0.14  |
| 1915                           | 0.21       | 0.09                            | 0.55  | 0.15  |
| 1925                           | 0.13       | 0.09                            | 0.70  | 0.08  |
| 1935                           | 0.10       | 0.14                            | 0.70  | 0.06  |

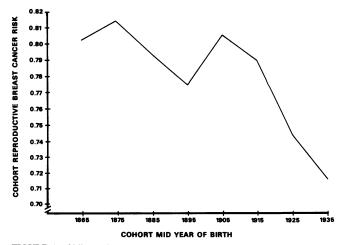


FIGURE 1—Childbearing Breast Cancer Risk in Connecticut Women, 1855-1945

breast cancer childbearing risk profiles (not shown here) derive from application of the relative risks from the large cohort study of Tulinius, et al, 14 and from the meta-analysis of White.<sup>20</sup>

# Breast Cancer Incidence and Age-Adjusted Incidence Ratios

Incidence among women age 40 and older has increased steadily, with possible interruption in the cohort of 1885 for 70 year old women, of 1895 for 60 year old women, and of 1935 for 40 year old women (Figure 2). (The study of Stevens, et al,<sup>2</sup> indicated a trough in the standardized incidence ratio between Connecticut cohorts of 1885 and 1895 and a possible decline following the cohort of 1925.)

The standardized incidence ratio in women 40 years and older showed a general increase from the earliest to the last cohorts (Figure 3). Only from the cohort of 1905 to that of 1915 was there a slight decline in the incidence ratio, followed again by an increase—a more gradual increase than that preceding the decline. Points of inflection showed a rather different pattern from Figure 11 in Stevens, et al,<sup>2</sup> principally because Stevens' model incorporated year of event (that is, the interaction between age and cohort). In addition, whereas Stevens, et al, considered women 20 years and older in five-year age and cross-section categories, we considered only women 40 years and older in 10-year age categories and 10-year cross-sections. Our study also includes three years of more recent data.

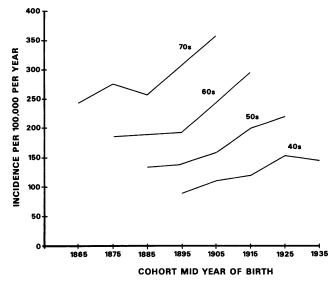


FIGURE 2—Breast Cancer Incidence in Connecticut Women Ages 40-79, by Mid-Cohort Year of Birth

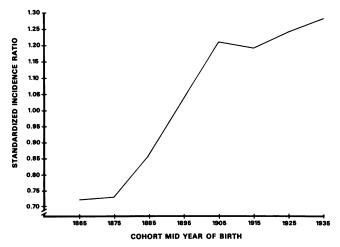


FIGURE 3—Standardized Incidence Ratio of Breast Cancer for Connecticut Women, 40 Years, by Mid-Year of Birth Cohort

# Childbearing Breast Cancer Risk and the Standardized Incidence Ratio

Comparison of cohort childbearing breast cancer risk (Figure 1) and the standardized breast cancer incidence ratio for the same cohorts (Figure 3) indicated clearly opposing trends. While childbearing proportions of cohorts would have predicted a general fall in incidence, a generally increasing trend was observed in the standardized incidence ratio. Indeed, higher predicted childbearing breast cancer risk was associated with lower actual incidence ratios, and vice versa.

Comparison of childbearing breast cancer risk (Figure 1) with age-specific incidence rates (Figure 2) also showed a general opposition of trends.

To review the comparisons made in prior population based studies of this issue<sup>7,15-20</sup> with evidence from the present data, we compared the standardized incidence ratio with each of the childbearing proportions—nulliparity, 2nd, 3rd, and 4th decade first births. Discernible relations were contrary to those hypothesized. For example, the proportion of 4th decade first births was unrelated to the standardized

incidence ratio, and the proportion of nulliparas was inversely related.

#### Discussion

This ecological study examines the association of basic reproductive events—childbearing and decades of first birth—with subsequent risk of breast cancer for all Connecticut women born between 1855 and 1945. Predicted changes are contrary to those observed. While changing childbearing patterns predict a general decline of breast cancer incidence from the cohort of 1865 to that of 1935, the standardized breast cancer incidence ratio generally increases.

These findings are consistent with the large population-based cohort study of Tulinius, et al, 14 in which nulliparity and age at first birth were significantly associated with breast cancer incidence within cohorts, but predicted incidence changes between cohorts contrary to those observed. It may be noted that international differences in childbearing patterns, e.g., nulliparity and early first births, likewise cannot explain the large international differences in breast cancer incidence or mortality, for example, the 4- to 5-fold differences between the US and Japan. 25,26 In fact, breast cancer mortality among US males is also roughly four times that of Japanese males, suggesting that factors unrelated to gender and childbearing history are important in determining international differences. 27

The conclusions of the present study do not contradict the association of nulliparity and age at first birth with breast cancer incidence. They suggest, however, that changes in breast cancer incidence among cohorts cannot be explained on the basis of changes in cohort childbearing. Cohortwise increases in breast cancer incidence, not only in Connecticut but elsewhere also, <sup>2</sup> have not been accounted for.

Several other recognized risk factors merit further consideration.

Age at Menarche and at Menopause: Early menarche and late menopause are recognized risk factors for breast cancer. <sup>13</sup> While age at menopause has remained relatively constant over the last century, <sup>28</sup> age at menarche has declined at a rate estimated at two months per decade, <sup>29</sup> thus suggesting an increase in breast cancer incidence.

Oophorectomy: Oophorectomy has been shown to be associated with subsequent decreased risk of breast cancer. <sup>13</sup> Armstrong <sup>16</sup> and others have attempted to show a negative association between rates of hysterectomy and breast cancer incidence. This comparison is misleading since it is not hysterectomy, but associated oophorectomy which affects breast cancer risk reduction. Changing rates of oophorectomy have not been examined for periods prior to 1960, <sup>30</sup> but this operation is probably rare and relatively recent, and thus is unlikely to be associated with the breast cancer changes considered here.

Oral Contraceptive Use: The effect of oral contraceptive use on subsequent breast cancer is a matter of controversy. Pike, et al, 31 have found that oral contraceptive use prior to first full term pregnancy increases the risk of breast cancer in young women (younger than 32 years). Vessey, et al, 32 and others 33 find no such effect. Despite their current prevalence, the recency of oral contraceptives precludes their association with the secular changes considered here.

First Trimester Abortion: The association of abortions prior to first full term pregnancy with increased risk of breast cancer in young women is also a matter of controversy<sup>32,33</sup> Documentation of abortion prior to the 1973 Supreme Court

decision is problematic, but this procedure has probably become widespread only recently, and thus again is unlikely to be associated with the changes considered here.

Multiparity: While multiparity and age at birth beyond the first have been found to have less effect on breast cancer than age at first birth, <sup>10,13</sup> studies of high parity populations indicate a strong effect. <sup>14,34,35</sup> In the US, rates of parity of two or more have generally increased since 1900, <sup>36</sup> suggesting a decline in breast cancer rates.

Lactation: While the international studies of MacMahon, et al,<sup>37</sup> had shown that, after controlling for parity, the effects of lactation in reducing breast cancer risk disappeared, recent studies again indicate an association, but principally in premenopausal women.<sup>38,39</sup> It is not clear how long-term secular changes in lactation could be assessed.<sup>40</sup>

Diet and Body Weight: Diet and one of its correlates, body weight, have been associated with international differences and secular changes in breast cancer rates.<sup>7,41</sup> Historical records of national and per capita consumption of different food products may allow exploration of the association of nutritional changes and changes in breast cancer incidence.

Electricity and Uninterrupted Light: There is experimental evidence in the rat that exposure to electro-magnetic fields or light reduces pineal production of melatonin; in turn; decreased production of melatonin leads to increased ovarian estrogen and pituitary prolactin production. Stevens<sup>42</sup> has hypothesized that increased exposure to light and electromagnetic fields may increase the risk of breast cancer in humans. Thus, it is interesting to speculate that increasing electrification may be responsible for some part of the observed secular trend. However, it is highly unlikely that the effect of electrification would be seen as changes in risk by cohort.

Secular trends and international differences in this common disease remain largely unexplained. The present study provides further evidence that prominent childbearing events in cohorts predict changes in cohort breast cancer contrary to those which have occurred. Other risk factors must counteract these cohort childbearing trends. Efforts should be made to identify modifiable risk factors which might explain cohort increases in breast cancer incidence.

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